DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: JAN 30 2004

From: Interdisciplinary Scientist/Pharmacist , Division of Dietary Supplement Programs , Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: ***Lactobacillus bulgaricus***

Firm: Kendy USA, LLC

Date Received by FDA: June 13, 2003

90-Day Date: September 11, 2003

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Gloria Cheng

95S-0316

RPT198

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

AUG 19 2003

Donna Bade, Attorney
Kendy USA LLC
704 Juniper Drive
Palatine, Illinois 60076

Dear Ms. Bade:

This is to inform you that the notification, dated June 9, 2003, you submitted on behalf of your client, Kendy USA LLC, pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on June 13, 2003. Your notification concerns the substance "*Lactobacillus bulgaricus*" that you assert will be a new dietary ingredient.

The notification claims that three specific strains of *Lactobacillus bulgaricus* will be used, and that they are referenced in the Bulgarian National Bank of Microorganisms and Cell Cultures as NBMCC 8243, 8244, and 8247. Subsequently, on July 29, 2003 we requested additional information in accordance with Title 21 of the Code of Federal Regulations (21 CFR) Part 190.69(d). We received your amendment on August 5, 2003. In the amendment, you agreed that the name of your substance should be "*Lactobacillus delbrueckii* subspecies *bulgaricus*" in accordance with Bergey's Manual of Determinative Bacteriology, 8th Edition. You clarified that your product is called "Biostim" and that "Lactoflor" is a registered trade mark name for the product used outside of North America. We will refer to your substance as "*Lactobacillus delbrueckii* subspecies *bulgaricus*" or "Biostim" in this letter.

You describe the substance as a low-lactose, freeze-dried, fermented milk product supplied as a chewable tablet, capsule, or a dissolvable powder, and that there will be less than 4,000,000 viable milk-acid *Lactobacillus delbrueckii* subspecies *bulgaricus* bacteria per gram (g). The recommended daily dosage is 6-12 grams per day, to be consumed orally as a chewable tablet, capsule with a small amount of fluid, or as a dissolvable powder. You state that it is suitable for adults and children over the age of three. In your amendment, you indicate that the level of the substance will be: chewable tablets will contain 0.8 g of Biostim and 0.8 g of inactive carrier and the capsules will contain 0.4 g of only "Biostim."

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement that contains a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient

will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

In accordance with 21 CFR 190.6(c), FDA must acknowledge its receipt of a notification for a new dietary ingredient. For 75 days after the filing date, your client must not introduce or deliver for introduction into interstate commerce any dietary supplement that contains the new dietary ingredient that is the subject of this notification.

Please note that acceptance of this notification for filing is a procedural matter, and thus, does not constitute a finding by FDA that the new dietary ingredient or supplement that contains the new dietary ingredient is safe or is not adulterated under 21 U.S.C. 342. FDA is not precluded from taking action in the future against any dietary supplement containing your new dietary ingredient if it is found to be unsafe, adulterated, or misbranded.

Your notification will be kept confidential for 90 days after the filing date of June 13, 2003 . After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any further questions concerning this matter, please contact Victoria Lutwak at (301) 436-2375.

Sincerely yours,

for Albert J. Moore

Susan J. Walker, M.D.
Acting Division Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

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SANDLER & TRAVIS
TRADE ADVISORY SERVICES
DETROIT • PORTLAND • OTTAWA
CONSULTING SERVICES

June 9, 2003

Via Overnight Mail

Division of Standards & Labeling Regulations
Office of Nutritional Products, Labeling and
Dietary Supplements (HFS_820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Pre-Market Notification for a New Dietary Ingredient

On behalf of our client, Kendy USA LLC ("Kendy") and pursuant to 21 CFR 190.6, Kendy is filing this pre-market notification of its intent to market a product (described herein as *Lactobacillus Bulgaricus)* as a new dietary ingredient. Kendy does not know whether this ingredient has been marketed in the United States prior to 1994 so it is submitting this notification as a precautionary measure. Kendy is aware that it is unable to market this product for a period of at least 75 days following the acceptance of this notification by the Food and Drug Administration ("FDA").

1. **Name and complete address:**

Kendy USA LLC
704 Juniper Drive
Palatine, IL 60074
Contact Person: Donna Bade, Attorney
Telephone: (312) 236-6555

8 46924

2. **New dietary ingredient:**

Probiotic *Lactobacillus Bulgaricus* strains:
NBMCC 8243*
NBMCC 8244*
NBMCC 8247*

- Strain references in Bulgarian National Bank of Microorganisms and Cell Cultures.

3. **Description of the dietary supplement that contains the new dietary ingredient:**

A. **Taxonomy:**

Lactoflor™ (Biostim series) is a low-lactose, freeze-dried, fermented milk product supplied as a chewable tablet, a capsule or a dissolvable powder

The active ingredient Lactobacillus Bulgaricus, (including the strains detailed above) is a natural probiotic and a member of the Lactobacillus family which includes Acidophilus, Casei, Johnsonii, Reuteri etc. These natural bacterium are widely available in tablet form & as foodstuffs (yogurt, cheese etc.) around the world, including the USA, with well documented benefits to human well being.

Typical composition of tablets/capsules:
Proteins – Oligopeptides, dipeptides & free amino acids.
Carbohydrates, Fats, Pectin, vitamins & minerals naturally found in milk.

B. **Level of the new dietary ingredient in the product:**

<4,000,000 viable milk-acid Lactobacillus Bulgaricus bacteria per gram.
Recommended daily dosage: 6-12 grams per day.

C. **Conditions of use if the product states in the labeling or if no conditions of use are stated, the ordinary conditions of use:**

Recommended as a dietary supplement. To be consumed orally as a chewable tablet, a capsule with a small amount of fluid or as a dissolvable powder. Suitable for adults and children over the age of 3.

D. **History of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe:**

1. **Reference to published materials attached:**

   Abstract 07E96 – Bulgarian Military Medical Acadamy, Sofia Institute for Aviation Medicine.

   Pirogov National Institute for Emergency Medicine, Sofia. Approval Record # 23/10.12.1986 by the Scientific Council of the Higher Military Medical Institute, Sofia, Bulgaria. Full report available upon request.

   Authorized for use by the Bulgarian Ministry of Health.

   Patent Office Registration – Republic of Bulgaria

2. **Confidential materials attached:**

   Quest Laboratories –Netherlands Analysis dated 4/29/03

   Confidential Product Characteristics

Please send all correspondence to:

Donna L. Bade
Attorney
Sandler, Travis & Rosenberg, P.A.
200 W. Madison St., Suite 2670
Chicago, IL 60606
Attorney for Kendy USA LLC

PATENT OFFICE
REPUBLIC OF BULGARIA

Document #: 5892
Date: 29.04.03

TO

KENDY LLC
Sofia
TO THE ATTENTION OF:
S. Kostadinov – President

Regarding your request (#5892/18.04.2003) for complete numerical research, we are attaching a copy of the biblio of IRN 742825 "LACTOFLOR".

Manager:

Dipl. Eng. Tzanka Petkova

Translation of major points:

1. The document is in French according to international agreements.
2. It is an international registration (ROMARIN).
3. Designations are 2-letter codes of countries as described on:
http://www.wipo.int/about-ip/en/ipworldwide/country.htm
(ex. ES = Spain)
4. Good/services are described at:
http://www.wipo.int/classifications/en/index.html

where 05 = Pharmaceutical and veterinary preparations; sanitary preparations for medical purposes; dietetic substances adapted for medical use, food for babies; plasters, materials for dressings; material for stopping teeth, dental wax; disinfectants; preparations for destroying vermin; fungicides, herbicides

and

30 = Coffee, tea, cocoa, sugar, rice, tapioca, sago, artificial coffee; flour and preparations made from cereals, bread, pastry and confectionery, ices; honey, treacle; yeast, baking-powder; salt, mustard; vinegar, sauces (condiments); spices; ice

and

32 = Beers; mineral and aerated waters and other non-alcoholic drinks; fruit drinks and fruit juices; syrups and other preparations for making beverages

COMPANY
SOFIA AD
TRANSLATION OFFICE
1000 Sofia 16 Pirotska Str.
telephone 983 35 18

Translation from Bulgarian

MILITARY MEDICAL ACADEMY – SOFIA
"PIROGOV" REPUBLICAN RESEARCH INSTITUTE OF EMERGENCY MEDICAL ATTENDANCE – SOFIA

Exposé of the Final Report on the Research of Methods of Food Therapy – Mixed Parenteral and Enteral Nutrition"

Approved by Record No 23/10.12.1986 by the Scientific Council of the Higher Military Medical Institute, Sofia, Bulgaria

Performed by: Higher Military Medical Institute – Clinic of Thermal Trauma and Clinic of Toxicology and Allergology, Sofia; "Pirogov" Republican Research Institute Of Emergency Medical Attendance – Sofia

Enteral food therapy was carried out with the low–lactose dry milk "Biostim" in a quantity of 550 g on the average, dissolved in lukewarm water up to 2500 ml daily. The composition of 100 g "Biostim LBS" dry product is given in Table 2.

Table 2

Fats	From 16.0 to 20.0 g
Proteins	From 23.0 to 27.0 g
Sugar total, inverted – incl. Lactose	From 43.0 to 47.0 From 0 to 4.0 g
Water	Up to 6.0 g
Energy Value	450 Kcal/1890 Kj
Minerals • Calcium • Potassium • Iron • Phosphorus • Other	Up to 6.0 g 1600 mg over 1500 mg 0.8 mg 780 mg
Vitamins • Vitamin A • Carotene • Vitamin D, Vitamin B1, Vitamin B2, Vitamin C etc.	 0.20 mg 0.25 mg

Viable Lactobacilus Bulgaricus cells – over 2500 per 1 g

Daily energy need of each patient were calculated according to Curery and Suderland's formulae.

- Curery – 25 Kcal x M/kg + 40 Kcal x % burnt area = necessary energy in Kcal per day.
- Suderland – 20 Kcal x M/kg + 70 Kcal x % burnt area = necessary energy in Kcal per day.

The daily need of proteins was calculated as per Suderland's formula: 1,0 g/ 0,16 g Nitrogen x M/kg + 3,0 g/0.48 g Nitrogen v % burnt area = g proteins per day.

Nitrogen balance was calculated as per Delbe's formula:
P x 0,14 = x ><y = uu x 0,59

Scientific Assignment: Clinical testing of methods of food therapy by means of mixed parenteral and enteral nutrition. Parenteral food therapy with Dextrose 10%, 20%, 50%; Aminozin 3,5%, 7%, 8,5%; Lipozin II 10%, 20%, manufactured by Abbot Co., USA; B/ Enteral food therapy with the low–lactose dry milk product "Biostim LBS" with pektin, manufactured by Lactina Ltd. Co., Sofia, Bulgaria.

Term: 01.01.1984 – 31.12.1986

Object of investigation: 34 patients with thermal trauma and 13 patients with serious toxo–allergic disorders – Layel's Syndrome and Stevens–Johnson's Syndrome; or a total of 47 patients.

A. Clinical testing in patients with thermal trauma: Clinical testing performed by Assoc.Prof. Ya.Ionov, M.D. Object of investigation were 34 patients with thermal trauma. The structure of cases under observation is given in Table 1. The quality of parenterally introduced substances are according to the given formulae and drawings. Lipid emulsions were introduced after the third day in compliance with the manufacturer's requirements.

Table 1

Structure of the cases under observation	
Total number	34 persons
Men	69%
Women	31%
Average age	39 ± 12 years
Average mass in kg	69 ± 13 kg
Average total area of the burn	40% ± 17%
Average area of deep burn	16% ± 15%
Face burn cases	69%
With progressive acute respiratory insufficiency (PARI)	31%
With sepsis	83%
With bronchopneumonia	41%
With bleeding curling ulcers	21%
Administered solutions: for parenteral nutrition "ABBOT"	Since 12±9 day
Mixed intubation + parenteral nutrition	85%
Intubation because of PARI	13%
Surgery performed	72%
Deceased	31%

ПАТЕНТНО ВЕДОМСТВО
НА РЕПУБЛИКА БЪЛГАРИЯ

ДО

ПАТЕНТНО ВЕДОМСТВО НА Р.БЪЛГАРИЯ
Изх. номер 5892 Дата 29.04.03
BULGARIAN PATENT OFFICE

КЕНДИ" ООД
гр. София
НА ВНИМАНИЕТО НА:
С. КОСТАДИНОВ- Управител

Относно Ваше искане за номерационно проучване с наш **Вх. № 5892/18.04.2003 год.**, приложено Ви изпращаме копие на библиографската справка на посочената от Вас марка **IRN 742825 "LACTOFLOR".**

Началник отдел РСТ заявки и ИУО:

инж. Цанка Петкова

1040 София, бул. "Д-р Г.М.Димитров"№ 52Б, тел. 7113 ххх, факс 708 325; 971 45 63-регистратура
БИН № 730 201 0001, Банков код код 661 966 11, Б-ва с/ка 300 017 090 7 БНБ - ЦУ в лева

111 NUMBER	742825
151 DATE	2000.05.29
171 PAID FOR	10 years
141 EXPIRATION DATE	2010.05.29
580 NOTIFICATION DATE	2000.11.02
450 PUBLICATION	GAZ 2000/21 (2000.11.23)
270 LANGUAGE	FR
540 MARK	**Lactoflor** Lactoflor
550 DETAILS	document with image; mark in color; color claimed;
531 VIENNA CLASSIF	27.05.01, 29.01.03
591 COLORS	Vert et blanc.
732 HOLDER	"KENDY" DROUJESTVO S OGRANITCHENA OTGOVORNOST 101, oulitsa "Sofia" BANKYA (BG) BG-1720 domiciled in BG
841 ORIGIN	BG
822 BASIC REG.	1999.08.06 36 172
831 DESIGNATIONS	AL, AM, AT, AZ, BA, BX, BY, CH, CN, CU, CZ, DE, DZ, EG, ES, FR, HR, HU, IT, KE, KG, KP, KZ, LI, LR, LS, LV, MA, MC, MD, MK, MN, MZ, PL, PT, RO, RU, SD, SI, SK, SL, SM, SZ, TJ, UA, UZ, VN, YU
511 NICE CLASSIF	05, 30, 32
511 GOOD/SERV	05 Produits pharmaceutiques; substances diététiques à usage médical; préparations de vitamines. 30 Pâtisserie et confiserie; additifs diététiques à usage alimentaire et non à usage médical, à base d'amidon, d'avoine, de riz, de blé, de céréales, y compris de mélanges de ces produits, produits sucrants, épaississants, essences aromatisantes, yaourt congelé, gelée royale, agents de liaison pour glaces. 32 Eaux minérales et gazeuses et autres boissons non alcooliques.
860 REFUSAL	KP Partial refusal of protection .. [GAZ 2001/10] 2001.04.30 Refusé pour tous les produits des classes 5 et 30. ES

Total refusal of protection

.. [GAZ 2001/13] 2001.06.21

KG

Acceptance / Grant of protection

.. [GAZ 2001/24]

All goods and services are affected

KP

Final decision confirming refusal of protection

.. [GAZ 2002/07] 2001.12.30

ES

Other final decisions

.. [GAZ 2002/14] 2002.04.30

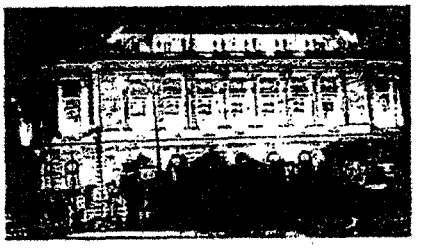
Admis pour tous les produits des classes 30, 32 et refusé pour tous ceux de la classe 5.

BALKAN MILITARY
MEDICAL COMMITTEE

Romanian National Board of
B.M.M.C.

The 4th CONGRESS of B.M.M.C.

ABSTRACT BOOK



National Military Circle Building

June 6 – 10, 1999
Bucharest, ROMANIA

ABSTRACT
07E96

Title: EFFECT OF THE BIOSTIM LBB YOGHOURT-TYPE PRODUCT ON LIPID METABOLISM IN AIR-FORCE AVIATORS

Author(s): Alexandrov, N., Petrov, A., Zlatev, R., Zhekova, M., Mikhaylova, Z., Kotseva, M. And Alexiev, L.

Institution: Military Medical Academy, Sofia Nstitution For Aviation Medicine

Sixty-for air-force pilots were selected for the study and divided into two groups. Biostim LBB was given to the subjects of values were measured in the beginning and at the end of the experiment: total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides.

The results were processed statistically and compared both between the two groups and with data collected throughout yearlong observation on the lipid status of military aviators.

The analysis of the data obtained allows us to conclude that the beneficial effect of Biostim LBB on lipid metabolism is more dependent on the duration of administration than on the daily dosage.

In the group where the subjects received a daily dose of 14 g of the preparation for 14 days, a trend towards increase in HDL cholesterol from 1.270 to 1.328 and decrease in LDL cholesterol from 4.399 to 4.212 was observed; however, these results were not statistically significant ($p>0.05$).

The group of subjects treated with the same daily dose of Biostim LBB for 30 days showed a statistically significant decrease in total cholesterol (from 7.100 to 6.053) and LDL cholesterol (from 4.322 to 3.852), while HDL cholesterol increased from 1.227 to 1.476. In both groups a decrease in triglyceride values was observed, but the decrease was not statistically significant.

THE EFFECT OF "BIOSTIM – LBS" ON THE FAT METABOLISM WITH PILOTS OF THE MILITARY AIR FORCES.

Fermentation by lactobacilli is one of the oldest methods, known by humanity, for milk processing and obtaining of the dairy products inextricably bound up with human nutrition. In the beginning of 20^{th} century the famous Russian scientist I.Mechnikov expressed the pre-assumption that Bulgarian`s longevity is partly due to the Yoghurt fermented by Lactobacillus Bulgaricus (LBB) consumption. The various researches in the previous decades and those from the last years show thatlactobacilli play an important role in human balanced nutrition and human health (8, 9, 11). Along with the other favourable effects, inclusively the anticancerogenic one (2, 4, 7) a well expressed hypolipedemic effect is established. The first hypolipedemic effect proofs of the products obtained by means of processing of milk with lactobacilli are met with the studies of G.Hepner et al, K.Schahani, B.Friend.

Given hypolipedemic effect proofs of the dairy products containing lactobacilli are established in the experimental researches of K.Schahani and G.Hepner and K.Schahan, P.Vankova-Petrova, 1998 and others. The researchers with us on volunteers in 1992 and 1993 by N.alexandrov and M.Zhekova and by M.Zhekova, K.Avramov and V.Gyosheva in 1994, as well as announcements from this year (1998) by L.Balabanski indicate a tendency of the lipids exchange parameters improvement, chiefly with respect to an decrease of the total level of the increased cholesterol, increase of the cholesterol level in the high density lipoproteins, decrease of the cholesterol in the low density lipoproteins, as well as a tendency towards normalization of the increased blood sugar – basic indicators for cardiac-vessel diseases appewarance and prophylactics.

MATERIAL AND METHODS

Subject of the research are 2 groups of volunteers, pilots from the MILITARY AIR FORCES of Bulgaria by profession, subjected to the characteristic for this profession hard physic strain and highly expressed stress factor. Both groups of volunteers composed of 23 persons each, have taken the Yoghurt product "BIOSTIM – LBS" produced by Bulgarian company. The latter product is a subject of a specific bio-technical production and is obtained from natural cow's milk. The "BIOSTIM-LBS" composition with pectin of 100 g. dry product is indicated in Table 1.

"BIOSTIM-LBS" WITH PECTIN
composition / content of 100 g. dry product

Table 1

CONTENT	IN GRAMS
1. FATS	From 16,0 to 20,0
2. PROTEINS	From 23,0 to 27,0
3. SUGAR inclusively lactosis	From 29,0 to 43,0
4. PECTIN	Up to 4,0
5. MINERALS CONTENT inclusively of (milligrams): - Calcium - Potassium - Iron - Phosphorus	Up to 6,0 1000 above 1500 0,8 780
6. VITAMINS CONTENT (milligrams): - Vitamin A - Carotin - Vitamin B-1, C and others	 0,20 0,25 0,25
7. ENERGY VALUE:	450 kcal / 1890 kJ

With the first group in the period 27.02.1998 till 10.03.1998 a daily dose of 25 g. of "BIOSTIM-LBS" has been taken in parallel with their ordinary pilots` nutrition regimen during a period of rest in the mountains. With the second group in the period 25.03.1998 till 03.05.1998 an average dose of 25 g. of the same product has been taken with the specific pilots` nutrition regimen during the physic and psychic strains characteristic for their everyday job at the airports.

The blood for the laboratory clinic tests was taken in the morning, before breakfast and after its respective pre-processing was tested immediately at the Military Medical Academy Central Clinic Laboratory. The determination of the total cholesterol was carried out by means of enzyme hydrolysis under the CHOL-PAP method with re-agents of the "CHUMANA" company and automatically recorded by means of "Spectrus-Abbot". The three-glycerides determination was carried out by means of enzyme hydrolysis with a subsequent determination of the glycerol by means of colometric three-stage reaction with reagents of the "POINTS" company and by recording with the same automatic analyzer. The cholesterol determination in the high density lipo-proteins (HDL-cholesterol) was done by means of precipitation with Phoshpho Volphrame acid and Magnesium dichloride and followed by a determination in the supernatant. The cholesterol in the low density lipo-proteins (LDL-cholesterol) was determined by means of calculation.

The referential limits of the total cholesterol are 4,0 – 6,2 mmol / L, of the tree-glycerides – up to 2,1 mmol / L, of the HDL cholesterol for men – above 0,9, of the LDL cholesterol – up to 3,5 mmol / L. The research results were statistically processed by means of variation analysis and by t criterium determination under Student-Fisher.

RESULTATS AND COMMENTS

The results of the tested parameters of the fat exchange with the I^{-st} group patients prior and after the Yoghurt product "BIOSTIM – LBS" with pectin intake are shown on Table 2.

RESULTS FROM THE FAT EXCHANGE PARAMETERS PRIOR AND AFTER THE "BIOSTIM-LBS" INTAKE - Ist GROUP

Table 2

ANALYSIS	CHOLESTEROL		HDL-CHOLESTEROL		LDL-CHOLESTEROL		THREE-GLYCERID	
statistic parameter	prior	after	prior	after	prior	after	prior	after
X	6,506	6,533	1,270	1,328	4,895	4,212	1,993	2,6
SD - x	0,871	1,218	0,297	0,280	0,797	0,932	1,350	1,4
t	0,172		0,556		0,576		1,216	
n	> 0,05		> 0,05		> 0,05		> 0,05	
	15		15		15		15	

As seen from the table, after the "BIOSTIM" intake there is a certain increase of the "good cholesterol" (HDH-cholesterol) values and decrease of the "bad cholesterol" (LDL- - cholesterol) values. It makes impression that with this Group the changes are statistically weekly reliable and indicate only a tendency. Actually the term oh the Yoghurt product "BIOSTIM – LBS" intake is evidently insufficient in order substantial changes in the fat exchange to trake place.

The results from the Fat Exchange Parameters research with the II-nd group Prior and After the Yoghurt Product "BIOSTIM" intake are shown on Table 3.

Table 3.

ANALYSIS	CHOLESTEROL		HDL-CHOLESTEROL		LDL-CHOLESTEROL		THREE-GLYCERID	
statistic parameter	prior	after	prior	after	prior	after	prior	after
- x	7,100	6,053	1,227	1,476	4,322	3,852	3,680	3,5
SD - x	1,900	1,658	0,658	0,436	1,093	0,998	1,286	0,9
t	2,609		2,219		2,230		1,07	
n	< 0,05 > 0,01		<0,05 > 0,01		<0,05 > 0,01		> 0,05	
n	15		15		15		15	

As is seen from the data stated in the Table after the "BIOSTIM" intake in the course of one month double longer period of time in comparison to the I^{-st} group there are available statistic differences in the total cholesterol values, of the HDL-cholesterol and LDL-cholesterol and statistically unreliable decrease of the three-glycerides values in the serum – in favourable for the organism changes.

CONCLUSIONS:

On the basis of the conducted scale research with pilots subjected to high physic and psychic strain and with their everyday nutritious regimen and way of living, the following conclusions can be drawn out:

1. The Yoghurt product "BIOSTIM" with pectin intake by pilots in the course of 2 weeks leads to a certain improvement of some fat exchange parameters which is statistically unreliable, but is only a tendency.
2. The Yoghurt product "BIOSTIM" with pectin intake by pilots in the course of more than 1 month leads to considerable statistically reliable change of the fat exchange parameters: Decrease of the total cholesterol, increase of the cholesterol in the high density lipo-proteins, decrease of the cholesterol in the low density lipo-proteins, as well as decrease of the three-glycerides level in the blood – parameters of the prophylactic effect on arterosclerotic vessel changes.
3. For the achievement of a durable effect from the products on the fat exchange its intake in doses of about 25 g per day-night in the course of at least 30 days is recommended.

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Via Overnight Mail

Division of Standards & Labeling Regulations
Office of Nutritional Products, Labeling and
Dietary Supplements (HFS_820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Aug. 4, 2003

Attn: Victoria Lutwak

Amendment Reference CTS-#84594
Pre-Market Notification for a New Dietary Ingredient

Dear Vickey:

On behalf of our client, Kendy USA LLC and in response to our conference call on Tuesday, July 29, 2003 with Dr. Linda Pellicore, Dr. Carolyn Young, Gloria Chang, yourself and Mark Rollinson of Kendy USA, we are submitting the following information with respect to the new dietary ingredient, Lactobacillus, Bulgaricus as agreed.

- **Statement changing species name:** We agree that the name should be Lactobacillus Delbrueckii Subspecies; Bulgaricus Strains NMBCC 8243, 8244 and 8247 according to Bergey's Manual of Determinative Bacteriology, Eighth Edition.
- **Statement regarding the relationship between Biostim, Lactoflor and Lactobacillus Bulgaricus:** The active, probiotic product is called Biostim. Lactoflor is a registered trade mark for the product used outside of North America.
- **ATTC Number**: We do not know this number.
- **Level of new dietary ingredient in the products:** Chewable tablets (1.6 mg) each contain .8 g of Biostim and .8 g of inactive carrier. The capsules (0.4g) contain only Biostim.
- **Recommended dosage**: 6-12 grams per day, but there is no risk of overdose and no observed side effects.
- **Safety reports:** Enclosed are the full reports previously furnished to you in abstract form and two additional reports—Balkan Military Medical Committee, "The Effect of the Biostim LBB Yoghourt-Type Product on Lipid Metabolism in Air-Force Aviators", and "Study of the Immunomodulating Effect of Selected Strains and Starter for Bulgarian Yoghurt."

We believe this is the supplemental information you requested. We are anxious to proceed as soon as possible. Please acknowledge receipt and advise our office with respect to the date for marketing our product.

85376

Respectfully,

Donna L. Bade
Thomas E. Johnson
Attorney
Sandler, Travis & Rosenberg, P.A.
200 W. Madison St., Suite 2670
Chicago, IL 60606
Attorney for Kendy USA LLC

COMPANY
SOFIA AD
TRANSLATION OFFICE
1000 Sofia 16 Pirotska Str.
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Translation from Bulgarian

MILITARY MEDICAL ACADEMY – SOFIA

DEPARTMENT OF TOXICOLOGY AND ALLERGOLOGY – CLINIC OF TOXICOLOGY AND ALLERGOLOGY WITH THE HIGHER MILITARY MEDICAL INSTITUTE – SOFIA

CLINIC OF TOXICOLOGY AND ALLERGOLOGY WITH THE NAVY HOSPITAL – VARNA

3, Georgi Sofiyski Str., Sofia

EXPOSÉ OF CLINICAL TESTING REPORT OF "BIOSTIM LBS" LOW-LACTOSE MILK-ACID PRODUCT FOR TREATMENT OF PATIENTS WITH VARIOUS INTOXICATIONS

SOFIA
1993

List of Performers:

1. Chief of Toxicology and Allergology Department
   Assoc.Prof. Nikola Alexandrov, Ph.D. (sgd.ill.)

2. Vassil Arnaudov, M.D., Senior Assistant Professor at Toxicology and
   Allergology Clinic, Sofia (sgd.ill.)

3. Marieta Georgieva, M.D., Senior Assistant Professor at Toxicology and
   Allergology Clinic, Varna (sgd.ill.)

(sgd.ill.)
Asoc.Prof. Dr.A,Andreev, Ph.D.
Deputy Chief of Education and Research Division of
Military Medical Academy
SEAL

Literature Summary

The review of specialized literature shows that in the last years greater part of the products for food therapy contain thermophilic lactobacilli. The results from the studied show that during milk–acid fermentation L.bulgaricus form substances, which enhance immune reactions and body resistance to morbid agents, i.e. they contribute to the more rapid recovery of patients with various disorders.

It is well known that of all nutrition products, milk is the most nourishing product and the best balanced, with regard to indispensable substances. During its absorption the body spends 3 or 4 times less energy compared to the bread albumen, and least gastric juice. The high nutritive value of milk is due to the optimal correlation of substances required for the nutrition of man, i.e. proteins, fats, carbohydrates, mineral salts, trace elements – calcium, magnesium, phosphorus, sodium, sulphur, chlorine and vitamins of the groups B, A, D, E, K. Colloidal state of albumen in cow milk guarantees its absorption in the body up to 95 %.

Under the influence of lactase enzyme, nearly 95% of the milk sugar, present in milk, may be hydrolized to glucose and galactose.

Milk fermentation with L.bulgaricus strains helps for the more rapid development of metabolic processes and the obtaining of larger quantities of free aminoacids di–, tri– and polypeptides, and thus for the better absorption of milk proteins by the body.

"LACTINA" Ltd. has at its disposal original strains LB Bio of L.bulgaricus type with proved anti–microbial qualities with regard to some pathogenic and conditionally pathogenic microorganisms.

Optimal nutrition should satisfy not only energy requirements, but through sufficient supply of macro–, microelements and vitamins, to ensure the normal course of complex vital processes in the body — oxidation, decomposition, synthesis of new substances, formation of hormones, passing of biostreams, heat regulation etc. For the quicker recovery of the patients, of particular importance is the relevant optimal nutrition. Exactly for this

purpose the product "Biostim LBS" has been developed in compliance with the medical and biological assignment of the Military Medical Academy.

I. MATERIAL AND METHODS

The performed biochemical analyses show that the technology for Biostim LBS manufacture guarantees balanced correlation of proteins, fats and carbohydrates (1,4:1:2,5). The correlation of casein to soluble albumen in Biostim LBS is 2,12:1, while in cow milk as a primary product is 4,52:1.
The performed amino–acid analysis shows that the correlation of independent amino-acids to the total quantity of amino acids in the various products is from 1:2,20 to 1:2,48 (taking into consideration that in order a protein to be nutritive, according to the World Health Organization this correlation has to be 1:2,08).

The performed gas–chromatographic analysis shows that the lipids of Biostim LBS contain the essential polyunsaturated fatty acids: caprone, caprilic and lauric acid, which, as it is known, have a high biological value. Therefore Biostim LBS ensures the supply of the body with such biologically active substances as the polyunsaturated and low–molecule fatty acids with essential amino–acids.

The analyses, carried out using Beoringer's tests, have shown that Biostim LBS contains large quantity of easily absorbed mono–saccharides glucose and galactose \from 13 to 16%), minimum quantities lactose and saccharose – up to 16 %.

Microbiological analysis has shown that in the different batches of Biostim LBS the content of viable cells of L.bulgaricus strain LBL 4 (a strain of proved prophicaltic and therapeutic qualities) is not less than 250 000 cells per gram.

The presence of minimum quantity of lactose makes this food suitable for application in patients with disturbed enzyme functions of the digestive system, resulting from the main disease.

The favourable biochemical and microbiological data mentioned above, have been clinical observed during the therapy of 234 patients and of another 86 patients suffering from various acute toxaemia, treated at the

clinics of toxicology of the Military Medical Academy in Varna – Navy Hospital, and in Sofia – Higher Military Medical Institute.

The period of observation was from 01.05.1991 till 31.12.1991. The above-mentioned group of patients included 38 patients of group intoxication, with toxic fumes during fire and 18 patients with respiratory intoxication with gasoline in a closed room.

For both groups of intoxication, leading have been the neurotoxic and hepatoxic changes of the body.

The distribution of patients with regard to sex is as follows: for Varna Clinic of Toxicology – 106 men (46,15%) and 128 women (53,85%) and for Sofia Clinic of Toxicology – 37 men (43,02%) and 49 women (56,98%). the patients of both clinics were from 16 to 80 years of age, adult patients for both clinics being 174. (74,25%) of the intoxication cases have been in medium and serious form, for Sofia clinic this distribution being among 52 patients (60,49%).

II. RESULTS AND DISCUSSION

Values of energy needs and supplied energy in Kcal per os and per venam for 186 patients with medium and serious forms of intoxication

Diagram 1

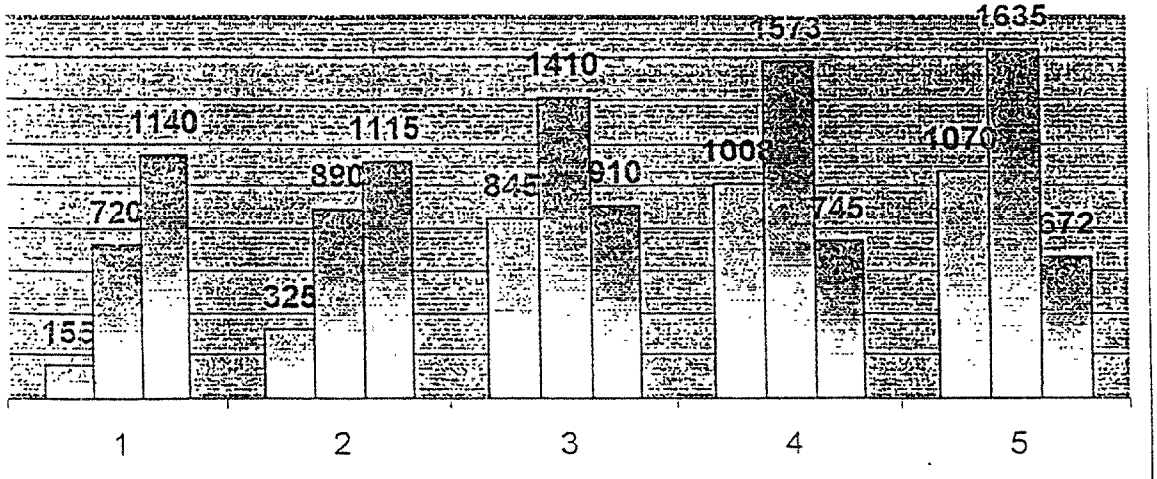


Diagram 1 gives the average energy values in Kcal supplied as food therapy per os and per venam for both groups of medium and serious form of intoxication till the 5th day of the hospital treatment.

Values of energy needs and supplied energy in Kcal per os and per venam for patients with serious forms of intoxication

Diagram 2

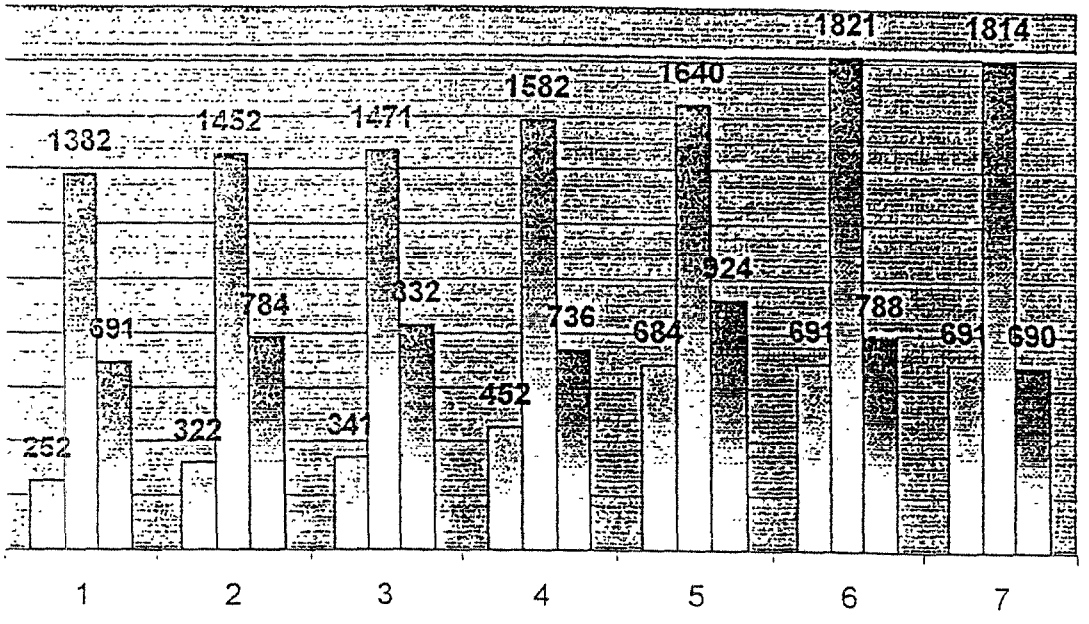


Diagram No 2 gives the same data for 48 serious cases in both clinics. Both diagrams give the values of supplied energy in Kcal per os by means of Biostim LBS. The data show that Biostim LBS satisfies an average of 45,36% of the energy supplied per os in the patients with medium and serious intoxication.

Level of proteins in patients with medium and serious forms of intoxication

Diagram 3

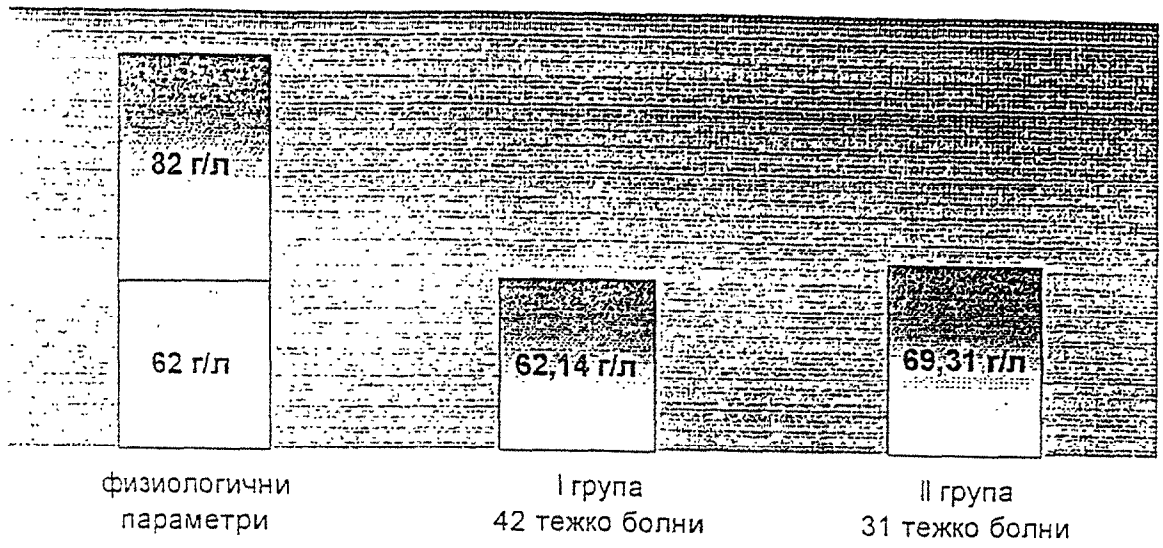


Diagram No 3 gives the proteinograms at dismissal of 42 serious cases and of 37 cases from the group of medium and serious intoxication. It is obvious that for both groups the level of proteins is preserved within physiological parameters, though near their lower limit.

Taking into consideration that one of the basic contemporary details, reflecting the correct approach to the therapy of serious cases, is the preservation of protein balance and energy needs, it can be definitely said that Biostim LBS creates a real possibility for correct diet of the serious cases including those from industrial accidents.

The milk–acid product Biostim LBS contains viable cells of Lactobacillus Bulgaricus, which influence beneficially the suffering organism, improving and regulating the internal microbial balance. They increase the body resistance to internal pathogenic microorganisms, modulate the immune system and have a favourable influence on liver encephalopathy. Of importance is also the milk acid produced by them, which has an anti–bacterial effect. During the clinical testing no side toxic or allergic effects have been established after Biostim LBS application.

The following can be said as a conclusion. Biostim LBS application as a food therapy contributes for improving body resistance by the balancing of the nutritive substances in the diet. The correct food therapy helps for

enhancing metabolic processes (mainly enzyme systems), attacked by the toxic substances, and has a positive effect on the functional state of some organs and systems, especially on liver functions. The milk–acid product Biostim possesses the relevant physico–chemical qualities, which bring it near the requirements for suitable nutrition of serious cases and at the same time surpasses the various foods used up till now. The analysis of biochemical parameters which register nitrogen metabolism in the body, shows that the milk–acid product Biostim may participate actively in the correction of negative nitrogen balance in mixed parenteral and enteral nutrition this way enhancing considerably recovery processes, reducing the hospital stay of patients and so having also economic effect. The above facts give us the right to recommend the use of the milk–acid product Biostim in the food therapy of serious cases due to serious, acute, exogenous intoxications.

The undersigned Tanya Kostadinova Kostova, certify that this is a true translation made by me from Bulgarian into English of the attached document .

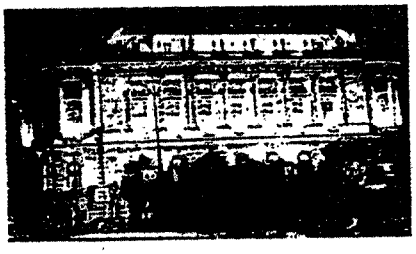
Translator:
Tanya Kostadinova Kostova

BALKAN MILITARY
MEDICAL COMMITTEE

Romanian National Board of
B.M.M.C.

The 4th CONGRESS of B.M.M.C.

ABSTRACT BOOK



National Military Circle Building

June 6 – 10, 1999
Bucharest, ROMANIA

ABSTRACT
07E96

Title: EFFECT OF THE BIOSTIM LBB YOGHOURT-TYPE PRODUCT ON LIPID METABOLISM IN AIR-FORCE AVIATORS

Author(s): Alexandrov, N., Petrov, A., Zlatev, R., Zhekova, M., Mikhaylova, Z., Kotseva, M. And Alexiev, L.

Institution: Military Medical Academy, Sofia Nstitution For Aviation Medicine

Sixty-for air-force pilots were selected for the study and divided into two groups. Biostim LBB was given to the subjects of values were measured in the beginning and at the end of the experiment: total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides.

The results were processed statistically and compared both between the two groups and with data collected throughout yearlong observation on the lipid status of military aviators.

The analysis of the data obtained allows us to conclude that the beneficial effect of Biostim LBB on lipid metabolism is more dependent on the duration of administration than on the daily dosage.

In the group where the subjects received a daily dose of 14 g of the preparation for 14 days, a trend towards increase in HDL cholesterol from 1.270 to 1.328 and decrease in LDL cholesterol from 4.399 to 4.212 was observed; however, these results were not statistically significant ($p>0.05$).

The group of subjects treated with the same daily dose of Biostim LBB for 30 days showed a statistically significant decrease in total cholesterol (from 7.100 to 6.053) and LDL cholesterol (from 4.322 to 3.852),. while HDL cholesterol increased from 1.227 to 1.476. In both groups a decrease in triglyceride values was observed, but the decrease was not statistically significant.

THE EFFECT OF "BIOSTIM – LBS" ON THE FAT METABOLISM WITH PILOTS OF THE MILITARY AIR FORCES.

Fermentation by lactobacilli is one of the oldest methods, known by humanity, for milk processing and obtaining of the dairy products inextricably bound up with human nutrition. In the beginning of 20th century the famous Russian scientist I.Mechnikov expressed the pre-assumption that Bulgarian's longevity is partly due to the Yoghurt fermented by Lactobacillus Bulgaricus (LBB) consumption. The various researches in the previous decades and those from the last years show thatlactobacilli play an important role in human balanced nutrition and human health (8, 9, 11). Along with the other favourable effects, inclusively the anticancerogenic one (2, 4, 7) a well expressed hypolipedemic effect is established. The first hypolipedemic effect proofs of the products obtained by means of processing of milk with lactobacilli are met with the studies of G.Hepner et al, K.Schahani, B.Friend.

Given hypolipedemic effect proofs of the dairy products containing lactobacilli are established in the experimental researches of K.Schahani and G.Hepner and K.Schahan, P.Vankova-Petrova, 1998 and others. The researchers with us on volunteers in 1992 and 1993 by N.alexandrov and M.Zhekova and by M.Zhekova, K.Avramov and V.Gyosheva in 1994, as well as announcements from this year (1998) by L.Balabanski indicate a tendency of the lipids exchange parameters improvement, chiefly with respect to an decrease of the total level of the increased cholesterol, increase of the cholesterol level in the high density lipoproteins, decrease of the cholesterol in the low density lipoproteins, as well as a tendency towards normalization of the increased blood sugar – basic indicators for cardiac-vessel diseases appewarance and prophylactics.

MATERIAL AND METHODS

Subject of the research are 2 groups of volunteers, pilots from the MILITARY AIR FORCES of Bulgaria by profession, subjected to the characteristic for this profession hard physic strain and highly expressed stress factor. Both groups of volunteers composed of 23 persons each, have taken the Yoghurt product "BIOSTIM – LBS" produced by Bulgarian company. The latter product is a subject of a specific bio-technical production and is obtained from natural cow's milk. The "BIOSTIM-LBS" composition with pectin of 100 g. dry product is indicated in Table 1.

"BIOSTIM-LBS" WITH PECTIN
composition / content of 100 g. dry product

Table 1

CONTENT	IN GRAMS
1. FATS	From 16,0 to 20,0
2. PROTEINS	From 23,0 to 27,0
3. SUGAR inclusively lactosis	From 29,0 to 43,0
4. PECTIN	Up to 4,0
5. MINERALS CONTENT inclusively of (milligrams): - Calcium - Potassium - Iron - Phosphorus	Up to 6,0 1000 above 1500 0,8 780
6. VITAMINS CONTENT (milligrams): - Vitamin A - Carotin - Vitamin B-1, C and others	 0,20 0,25 0,25
7. ENERGY VALUE:	450 kcal / 1890 kJ

With the first group in the period 27.02.1998 till 10.03.1998 a daily dose of 25 g. of "BIOSTIM-LBS" has been taken in parallel with their ordinary pilots` nutrition regimen during a period of rest in the mountains. With the second group in the period 25.03.1998 till 03.05.1998 an average dose of 25 g. of the same product has been taken with the specific pilots` nutrition regimen during the physic and psychic strains characteristic for their everyday job at the airports.

The blood for the laboratory clinic tests was taken in the morning, before breakfast and after its respective pre-processing was tested immediately at the Military Medical Academy Central Clinic Laboratory. The determination of the total cholesterol was carried out by means of enzyme hydrolysis under the CHOL-PAP method with re-agents of the "CHUMANA" company and automatically recorded by means of "Spectrus-Abbot". The three-glycerides determination was carried out by means of enzyme hydrolysis with a subsequent determination of the glycerol by means of colometric three-stage reaction with reagents of the "POINTS" company and by recording with the same automatic analyzer. The cholesterol determination in the high density lipo-proteins (HDL-cholesterol) was done by means of precipitation with Phoshpho Volphrame acid and Magnesium dichloride and followed by a determination in the supernatant. The cholesterol in the low density lipo-proteins (LDL-cholesterol) was determined by means of calculation.

The referential limits of the total cholesterol are 4,0 – 6,2 mmol / L, of the tree-glycerides – up to 2,1 mmol / L, of the HDL cholesterol for men – above 0,9, of the LDL cholesterol – up to 3,5 mmol / L. The research results were statistically processed by means of variation analysis and by t criterium determination under Student-Fisher.

RESULTATS AND COMMENTS

The results of the tested parameters of the fat exchange with the I^{-st} group patients prior and after the Yoghurt product "BIOSTIM – LBS" with pectin intake are shown on Table 2.

RESULTS FROM THE FAT EXCHANGE PARAMETERS PRIOR AND AFTER THE "BIOSTIM-LBS" INTAKE - Ist GROUP

Table 2

ANALYSIS	CHOLESTEROL		HDL-CHOLESTEROL		LDL-CHOLESTEROL		THREE-GLYCERID	
statistic parameter	prior	after	prior	after	prior	after	prior	after
X	6,506	6,533	1,270	1,328	4,895	4,212	1,993	2,6
SD - x	0,871	1,218	0,297	0,280	0,797	0,932	1,350	1,4
t	0,172		0,556		0,576		1,216	
n	> 0,05		> 0,05		> 0,05		> 0,05	
	15		15		15		15	

As seen from the table, after the "BIOSTIM" intake there is a certain increase of the "good cholesterol" (HDH-cholesterol) values and decrease of the "bad cholesterol" (LDL- - cholesterol) values. It makes impression that with this Group the changes are statistically weekly reliable and indicate only a tendency. Actually the term oh the Yoghurt product "BIOSTIM – LBS" intake is evidently insufficient in order substantial changes in the fat exchange to trake place.

The results from the Fat Exchange Parameters research with the II-nd group Prior and After the Yoghurt Product "BIOSTIM" intake are shown on Table 3.

Table 3.

ANALYSIS	CHOLESTEROL		HDL-CHOLESTEROL		LDL-CHOLESTEROL		THREE-GLYCERID	
statistic parameter	prior	after	prior	after	prior	after	prior	after
- x	7,100	6,053	1,227	1,476	4,322	3,852	3,680	3,5
SD - x	1,900	1,658	0,658	0,436	1,093	0,998	1,286	0,9
t	2,609		2,219		2,230		1,07	
n	< 0,05 > 0,01		<0,05 > 0,01		<0,05 > 0,01		> 0,05	
n	15		15		15		15	

As is seen from the data stated in the Table after the "BIOSTIM" intake in the course of one month double longer period of time in comparison to the I^{-st} group there are available statistic differences in the total cholesterol values, of the HDL-cholesterol and LDL-cholesterol and statistically unreliable decrease of the three-glycerides values in the serum – in favourable for the organism changes.

CONCLUSIONS:

On the basis of the conducted scale research with pilots subjected to high physic and psychic strain and with their everyday nutritious regimen and way of living, the following conclusions can be drawn out:

1. The Yoghurt product "BIOSTIM" with pectin intake by pilots in the course of 2 weeks leads to a certain improvement of some fat exchange parameters which is statistically unreliable, but is only a tendency.
2. The Yoghurt product "BIOSTIM" with pectin intake by pilots in the course of more than 1 month leads to considerable statistically reliable change of the fat exchange parameters: Decrease of the total cholesterol, increase of the cholesterol in the high density lipo-proteins, decrease of the cholesterol in the low density lipo-proteins, as well as decrease of the three-glycerides level in the blood – parameters of the prophylactic effect on arterosclerotic vessel changes.
3. For the achievement of a durable effect from the products on the fat exchange its intake in doses of about 25 g per day-night in the course of at least 30 days is recommended.